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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,981	03/22/2001	Gary DeJong	24601-416B	7622

7590 05/17/2004

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S/M.

Office Action Summary	Application No.	Applicant(s)	
	09/815,981	DEJONG ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,30 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,6-8,11-16 and 30* is/are rejected.

7)☒ Claim(s) *5,9,10 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *30 March 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 March 2004 has been entered.

Claims 1-16 and 30 were pending and under consideration in the previous Office Action. Claim 1 was amended and claim 33 was added in the Paper filed 30 March 2004. Claims 1-16, 30 and 33 are pending and under consideration.

Response to Amendment

Double Patenting

Rejection of claims 1-16 and 30 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-8, 11-16 and 30 of copending Application No. 10/086,745 is withdrawn in view of cancellation of the conflicting claims in the '745 application.

Claim Rejections - 35 USC § 112

Rejection of claims 1-4, 6-16 and 30 under 35 U.S.C. 112, first paragraph, as lacking enablement is withdrawn in view of applicants arguments and the art made of record in the information disclosure statement filed 30 March 2004.

Claim Rejections - 35 USC § 103

Claims 1-4 and 11-15 stand rejected under 35 U.S.C. 103(a) as unpatentable over either one of Felgner *et al.* or Zelphati *et al.* in view of Nolan *et al.* for reasons of record and herein below in the response to arguments.

Response to Arguments

Claim Rejections - 35 USC § 103

In response to the *prima facie* case and arguments of record, Applicant has amended the claims such that they are now limited to the method wherein intact and condensed labeled large nucleic acid molecules are introduced and remain intact and condensed after delivery. Applicant urges throughout the arguments that the cited art does not teach these limitations. These arguments have been fully considered but are not deemed persuasive.

Applicant points to several teachings in the specification to support the newly added limitations including: page 34, lines 8-1 3; page 47, lines 18-20; page 51, lines 9-10; page 52, lines 29-31; and page 54, lines 4-6. However, none of these teachings provide a limiting definition of intact or condensed. As large DNA molecules, such as those of the instant claims, will essentially always contain some discontinuities in the phosphate backbone, it is unlikely that the nucleic acid must be absolutely intact. However, there is no teaching in the specification to indicate at what point a nucleic acid is no longer "intact" as recited in the claims. Therefore, the limitation is interpreted to broadly read on any nucleic acid that is sufficiently intact to provide the desired function (*i.e.*, expression). As discussed in previous Office Actions, the cited art teaches that the introduced nucleic acids should provide for expression of genes encoded thereby

and therefore is "intact" as the limitation is understood. Likewise, the specification provides no indication as to the extent to which a given DNA must be condensed to meet the limitation set forth in the claim. It would be extremely uncommon for a nucleic acid of 500 kb to be free of any condensation (*i.e.*, completely linear). Therefore, all DNAs are condensed to some extent. Furthermore, Nolan *et al.* clearly teaches that it is preferred that chromosomes to be introduced into cells be maintained in a condensed (metaphase) state (see especially the second full paragraph on page 9). Therefore, condensation of the nucleic acid is not only inherent, it is explicitly taught in the art. Finally, with regard to the limitation that the nucleic acid molecules remain intact and condensed after delivery, the disclosure provides no indication as to how long a nucleic acid molecule must remain intact and condensed after delivery to meet the limitation. As any nucleic acid molecule that is intact and condensed at the time it is delivered to the cell will remain that way for some finite period of time after delivery, even if only briefly, the intact and condensed nucleic acid molecules described in the cited art can reasonably be expected to remain that way after delivery. For these reasons, the newly added limitations do no distinguish the claimed invention from the art of record.

In addition to arguments based on the new "intact and condensed" limitation, applicant argues that there is no evidence of any suggestion in an of the cited references for modifying labeling techniques so they are applicable to large nucleic acid molecules. However, as discussed in previous Office Actions, Felgner and Zelphati *et al.* teach a method of labeling DNA with a fluorescent tag such that the DNA remains competent to express a gene encoded thereby while Nolan *et al.* teaches a method of introducing fluorescently tagged large DNA into a cell. There is nothing in the teachings of the cited art that would dissuade the skilled artisan from combining

the teachings found therein and, given the desirability of fluorescently labeled artificial chromosomes as a gene transfer vehicle taught by Nolan *et al.* and the desirability of the method described by Felgner *et al.* and Zelphati *et al.* as a means to fluorescently label nucleic acids such that they remain functionally intact (see *e.g.*, the Office Action mailed 16 December 2002, page 14), the skilled artisan would be motivated to combine the teachings of the art according to the limitations of the instant claims.

In response to the assertion in the previous Office Action that there is no reason to believe that the small DNAs taught by Felgner *et al.* and Zelphati *et al.* are any different from the chromosomes of Nolan *et al.*, Applicant argues, "Nolan *et al.* points out, however, small and large DNAs can differ; for example, delivery of chromosomes, due to their size, is very difficult by any method and that methods used for smaller DNAS, might not be suitable for large nucleic acids" and "there is no teaching or suggestion in the cited references, singly or in any combination, that techniques for labelling nucleic acids, introducing labelled nucleic acids into cells and measuring gene expression from labelled nucleic acids that are suitable for small DNAs would be adaptable to large nucleic acids." However, it should be made clear that the previous Office Action actually states, "Applicant has provided no reason to believe that the large DNAs taught by Nolan *et al.* are substantially different from the smaller DNAs of Felgner *et al.* and Zelphati *et al.* with respect to the successful application of PNA labeling." (page 20, emphasis added). In other words, there is no reason to believe that method of labeling a nucleic acid taught by Felgner *et al.* and Zelphati *et al.* is size dependent. With regard to delivering a large nucleic acid into a cell, Nolan *et al.* provides detailed instruction on how a labeled large nucleic acid can be delivered into a cell. Therefore, the skilled artisan in possession of the teachings of Nolan *et*

al. would have a reasonable expectation of success in delivering a labeled large nucleic acid into a cell.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 U.S.C. §103.

New Grounds

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 6-8, 14, 16 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Felgner *et al.* (1999) WO 99/13719 in view of Nolan *et al.* (2000) WO 00/34436 and further in view of Giese *et al.* (1998) U.S. Patent No. 5,747,338.

Claims 6-8 depend from claim 1 and are directed to embodiments of the method wherein the reporter gene is selected from various genes routinely used as marker genes including GFP. Upon further review it was found that Felgner *et al.* teaches the method for determining the delivery and expression of a nucleic acid introduced into a cell wherein the reporter gene is GFP. Because Felgner *et al.* explicitly teaches that GFP can be used in the method for detecting or determining delivery and expression of a nucleic acid described therein, it would have been obvious to one of ordinary skill in the art at the time of filing to use a GFP reporter gene in the method of Felgner *et al.* in view of Nolan *et al.* for the reasons set forth in previous Office Actions regarding claim 1. Furthermore, Giese *et al.* teaches that the other reporter genes set forth in the claims were conventional in the art at the time of filing (see especially the second full

paragraph in column 6) and, absent evidence to the contrary, would be functionally equivalent to the GFP of Felgner *et al.* for the purposes of determining delivery and expression of a nucleic acid into a cell.

Claims 16 is directed to the method of claim 14 and claim 30 is directed to the method of claim 1 wherein the cells are stem cells or embryonic cells. Nolan *et al.* teaches that the method of delivering a labeled large nucleic acid into a cell disclosed therein is particularly useful for generating transgenic animals (see especially the second paragraph on page 1). One of ordinary skill in the art at the time of filing would know that any method of generating a transgenic animal would require that the nucleic acid be introduced into an embryonic stem cell. Therefore, the limitations of the instant claims 16 and 30 would be obvious to one of ordinary skill in the art at the time of filing for reasons of record regarding claims 1 and 14.

Allowable Subject Matter

Claims 5, 9, 10 and 33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

DAVID GUZO
PRIMARY EXAMINER